Title

Radiological evaluation of calcium hydroxylapatite implantation to correct volume loss in the dorsum of the hand

Authors

Amir Moradi, MD, MBA[1], Heather P. Lampel, MD, MPH[2], Birgit Flatau-Baque, Ph.D.[3], Gemma Odena, Ph.D.[2]

Affiliations

[1] Private Practice, Vista, California

[2] Merz North America, Inc., Raleigh, North Carolina, U.S.A.

[3] Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany

Corresponding author

Name: Amir Moradi

Mailing address: 2023 West Vista Way, Vista, CA 92083

E-mail address: moradimd@gmail.com

Telephone number: +1-760-645-1309

Keywords

Calcium hydroxylapatite, radiology, Radiesse, safety, soft tissue fillers

Short title

Calcium hydroxylapatite safety in dorsal hands

Clinical Trial Registration

NCT02904096

https://clinicaltrials.gov/ct2/show/NCT02904096?id=NCT02904096&rank=1&load=cart

Conflicts of Interests

This study was sponsored by Merz Pharmaceuticals GmbH, Frankfurt am Main, Germany. Dr. Moradi is a consultant and advisory board member for Merz North America, Allergan, Galderma, and Skin Medica. Additionally, Dr. Moradi acts as a consultant and speaker for BTL, Lutronic, Alastin, and is an honorarium recipient from Evolus.

Abbreviations

AE: adverse event; AP: anteroposterior; CaHA: Calcium hydroxylapatite; CT: computed tomographic scans; FDA: Food and Drug Administration; GAIS: Global Aesthetic Improvement

Scale; MHGS: Merz Hand Grading Scale; MHQ: Michigan Hand Outcomes Questionnaire; MRI: Magnetic resonance image; SD: standard deviation; SES: safety evaluation set.

Abstract

Background

Calcium hydroxylapatite (CaHA) is a radiopaque dermal filler used to provide volume correction in the dorsal hands.

Objective

To evaluate whether CaHA implantation in the dorsum of the hands interferes with radiological assessment by obscuring the bones.

Methods & Materials

This prospective, single-center, open-label study enrolled 20 subjects with Merz Hand Grading Scale (MHGS) grades ranging from moderate (MHGS 2 or 3; n=10) to very severe (MHGS 4; n=10). All subjects received one CaHA injection and were offered up to three retreatments. Bone obscuration was assessed by a blinded radiologist interpreting plain radiographs (X-rays). MHGS was evaluated and subjects self-assessed using a Global Aesthetic Improvement Scale.

Results

No bone obscuration was reported at any evaluated time point. Foreign material was present in 100% of hands on Month 1 X-rays and in 83.3% of hands on Month 24 X-rays.
AEs reported in 30% of subjects were injection-site abnormalities of mild to moderate severity.

All subjects achieved ≥ 1-point improvement on the MHGS at Month 1 and subjects in both groups reported aesthetic improvements.

Conclusion

Treatment with CaHA in the dorsal hands is well tolerated, improves the overall aesthetic appearance of the hands, and does not obscure radiographic assessment of the bones in X-rays up to 24 months after initial injection.

Introduction

The hands are a highly visible part of the body subject to visible aging at approximately the same rate as the face [1]. With aging, the hands suffer a loss of dorsal subcutaneous tissue which then accentuates the appearance of tendons and veins [1].

In 2015, calcium hydroxylapatite (CaHA) became the first Food and Drug Administration (FDA)-approved filler available for rejuvenation of the aging hand. CaHA is the principal component of Radiesse® Injectable Implant, an opaque, sterile, non-pyrogenic, semi-solid, cohesive implant [2]. CaHA is chemically identical to the calcium component of bones and teeth, giving the product a high degree of biocompatibility [3]. CaHA has been safely used for over 20 years in applications across specialties including orthopedics, neurosurgery, dentistry, otolaryngology, and ophthalmology [4, 5].

The available literature supports both the safety and effectiveness of CaHA injection for hand rejuvenation [4-8]. Volume restoration in the hands provides a more youthful appearance, reducing skin laxity and wrinkling, and decreasing the prominence of underlying structures such as tendons and veins [9]. Multiple authors report immediate, favorable results following CaHA injection with durable results lasting up to 12 months, noting both physician and patient satisfaction [1, 3, 10-13]. CaHA injection in the hands has been associated with minor adverse

events such as swelling, edema, pain, bruising, and redness. Generally these events resolved within two weeks [12-14].

The radiodensity of CaHA is similar to that of bone and has been visualized on maxillofacial radiographic examinations, computed tomographic (CT) scans, ultrasounds, and on magnetic resonance images (MRIs) [3, 4, 8, 15, 16]. A previous evaluation of CaHA implantation demonstrated its radiopacity and a lack of overt radiographic safety concerns in a study of 58 patients after facial implantation, with CaHA not always being visible on plain X-rays [17]. The study concluded that it is unlikely that CaHA would be confused in practice with standard abnormalities and aberrant radiographic findings in the face.

The objective of this prospective, single-center, open-label study was to evaluate whether CaHA implantation in the dorsum of the hands interfered with radiological assessment by obscuring the bones. The hypothesis was that the radiographic appearance of CaHA in the hands does not obscure the appearance of the bones of the hands as seen on standard, plain radiography (X-rays) of the hand.

Methods

Study design

This was a two year, prospective, single center, open-label, descriptive study designed to evaluate the safety and effectiveness of CaHA injection (Radiesse®; Merz, Raleigh NC, US) into the dorsum of the hands. The chosen CaHA implant is an injectable, opaque, sterile, non-pyrogenic, semi-solid, cohesive implant. The study was conducted according to the ethical guidelines of the Declaration of Helsinki and in compliance with the International Conference on Harmonization and Good Clinical Practice principles.

Participants

Enrolled subjects had baseline dorsal Merz Hand Grading Scale (MHGS) grades ranging from moderate to very severe volume loss [18, 19]. Grade 4 hands were defined as a very severe loss of fatty tissue and marked visibility of veins and tendons in the dorsal hand. Grade 2 or 3 hands were defined as a moderate to severe loss of fatty tissue and mild to moderate visibility of veins and tendons in the dorsal hand. Subjects in Group A were required to present with MHGS grade 4 in at least one hand at baseline. The other hand could show a MHGS grade of 4, 3 or 2. Subjects in Group B were required to present with MHGS grade 2 or 3 in both hands at baseline. To be included in the study, subjects must have been healthy male or non-pregnant female ≥ 22 years old. Written informed consent

was obtained and enrolled subjects accepted the obligation not to receive any other procedures in the dorsum of the hands through the end of the study. Exclusion criteria are described in Table 1.

Treatments administered

CaHA mixed with 2% lidocaine HCl was administered in the dorsum of the hands. All subjects received at least one CaHA injection and were offered up to three retreatments (at Month 6, Month 12 and Month 18). Subjects received injections in both their hands.

Subjects were required to present for a total of up to 15 visits and four follow-up phone calls (Figure 1). Of these visits, 7 to 10 were in-office investigational site visits, an additional 3 to 5 were X-ray visits at a licensed radiology center, and 1 to 4 were follow-up phone calls during their 24-month study participation. The fourth X-ray visit was only required at Month 12 if obscuration was present in the 6 month X-ray, and the fifth X-ray visit was only conducted if a subject received all four total CaHA treatments.

Endpoints

The primary safety endpoint of the study was the incidence of obscuration of the bones on X-rays of the hand as noted by two blinded, licensed radiologists at 1, 6, 12, and 24 months following injection of CaHA in the dorsum of the hand. Obscuration was defined as any hand X-ray that a blinded radiologist interpreted as CaHA obscuring bones.

Secondary endpoints included: rate of device/injection-related severe adverse events (AEs) reported by the study investigator at 1 and 6 months following CaHA injection; Michigan Hand Outcomes Questionnaire (MHQ) scores based on investigator's assessment at baseline and study exit; proportion of subjects with MHGS improvement of ≥ 1 point in both hands by a masked evaluator at 1 and 6 months after initial treatment or retreatment; and subject's satisfaction on the Global Aesthetic Improvement Scale (GAIS) at 1 and 6 months after initial treatment or retreatment.

Assessments

Standard, plain radiographs (X-rays) of anteroposterior (AP) and lateral views were taken at a licensed radiographic imaging center at baseline, 1 and 6 months following initial injection for all subjects. If bone obscuration was present in the 6 month X-rays, then additional X-rays were required at 12 months following initial injection. Only subjects who received all four study treatments had X-rays taken at 24 months following initial injection (Figure 1). Bone obscuration was only evaluated in hands with foreign material present in the X-rays.

AEs were documented by study investigators. A take-home diary was dispensed to study subjects to collect common treatment site responses (CTRs) for 30 days post-injection.

Subjective hand-functional outcomes were assessed by study investigators using a validated MHQ questionnaire. In this study, MHQ function and pain scores were assessed. Higher

MHQ function scores indicate better hand performance while higher MHQ pain scores indicate more pain [20].

In addition, MHGS was assessed by study investigators to measure efficacy of CaHA injection, and subjects self-assessed aesthetic outcomes using a GAIS scale.

Sample size and statistical analysis methods

Twenty evaluable subjects were planned for this study. The sample size was chosen to provide a clinically relevant sample to characterize radiologic evaluations after dorsal hand treatments with CaHA while preventing unnecessary subject exposure to radiation.

All analyses were performed on the safety evaluation set (SES; all subjects who received at least one injection). AEs were coded according to the Medical Dictionary for Regulatory Activities. Only treatment emergent AEs (TEAE) were analyzed, i.e., AEs with onset/worsening after the first injection up to and including the end of study visit.

The primary event of interest was whether treatment with CaHA interfered with radiological assessment by obscuring the bones of the hand at any time during the study. Corresponding 95% exact binomial confidence intervals (CIs) for the percentage of subjects with bone obscuration in at least one hand by visit were calculated.

Results

Subject demographics

The study was conducted at a single site in the United States. Ten subjects with very severe volume loss (MHGS grade 4 in one or both hands; Group A) and 10 subjects with moderate to severe volume loss (MHGS grades 2 or 3 in both hands; Group B) received the initial CaHA injection. All subjects received treatment in both hands.

All enrolled subjects were female; the mean (standard deviation, SD) age in Group A was 61.6 (7.40) years and was 53.3 (9.83) years in Group B, and 95% of all enrolled subjects identified their race as white (Table 2).

Extent of exposure

All subjects (20 subjects, 40 hands) received the initial treatment. In Group A (10 subjects, 20 hands), 16 hands were rated as MHGS grade 4, and four (4) hands were rated as MHGS Grade 3. In Group B (10 subjects, 20 hands), 14 hands were rated as MHGS grade 3, and six (6) hands were rated as MHGS grade 2. Eleven subjects (55%) received retreatment at 6 months, 16 (80%) were retreated at 12 months, and 11 (55%) were retreated at 18 months. Six subjects (30.0%) received the initial CaHA injection and all three retreatments offered (Table 3). All subjects completed the study through the 24-month visit.

Injection volumes were recorded as the sum of total volumes of CaHA (up to a maximum of 3 cc) and lidocaine (up to 0.52 cc) injected. No subject was injected with more than 3 cc of CaHA per hand per (re)treatment session. The mean initial injection volume ranged from 3.34 cc (CaHA plus lidocaine) in Group A to 2.64 cc in Group B (Table 4).

In general, as expected, mean injection volumes were higher for Group A at initial injection, Month 12 retreatment, and Month 18 retreatment. Mean injection volumes were similar for both groups at Month 6 retreatment.

Safety results

For all subjects, the initial X-rays, made before any injection, showed no foreign material. Foreign material was present in all hands (100%) on Month 1 X-rays (Table 5). At Month 6, foreign material was present in 85% of left hands and in 80% of right hands on the lateral view and in 85% of left hands and in 90% of right hands on the AP view. At Month 24, it was present in 83.3% of hands in subjects who received all treatments.

No obscuration of the bones was reported in either hand (left or right) for either view (AP or lateral) at any evaluated time point.

Overall, 14 subjects (70%) experienced a total of 28 TEAE. Six subjects (60%) experienced a total of 9 TEAEs in Group A and 8 subjects (80%) in Group B experienced 19 TEAEs. Only 2 TEAEs reported for 2 subjects (20%) in Group A and 12 TEAEs for 4 subjects (40%) in Group B were possibly or definitely related to the study device or injection procedure.

These possibly or definitely related TEAEs were injection site abnormalities of mild to moderate severity, such as swelling, pain, or nodule (Table 6). There was only one subject in Group B who experienced related severe swelling in both hands at 15 days after the initial injection with CaHA and again at 29 days after Month 18 re-treatment. No serious AEs were reported, and no subject withdrew from the study because of an AE.

A take-home diary was dispensed to study subjects to collect CTRs for 30 days post-injection. Following initial CaHA injection, most subjects reported swelling (100%), redness (90%), bruising (85%), and pain (80%) in their 30-day diaries (Table 4).

Overall mean function scores at the end of the study (Month 24, left hand: 99.8 and right hand: 100) were higher than at baseline (left hand 95.3 and right hand 97.8). Moreover, for those subjects who received all four treatments (n = 6) mean function scores (left hand: 99.2 and right hand: 100) were also higher than at baseline.

Similarly, mean pain scores at the end of the study (Month 24, left hand: 0.0 and right hand: 0.5) were lower than at baseline. In addition, for those patients who received all four treatments mean pain scores (left hand: 0.0 and right hand: 1.7) were also lower than at baseline.

Efficacy results

MHGS results showed ≥ 1-point improvement from baseline in all subjects in both groups at Month 1. At Month 6 after the first injection, 8 subjects (80%) in Group A and 9 subjects (90%) in Group B continued to show a ≥ 1-point improvement from baseline (Figure 1).

In general, subjects in both groups reported improvements in the overall aesthetic appearance of the hands when compared to baseline. At Month 1, 100% of subjects in Group A and Group B indicated they achieved some level of improvement. At Month 6 after the first injection, 90% of subjects in Group A and Group B reported some level of improvement.

Discussion

Overall, the results of this this single-center, open-label, descriptive, post-approval study demonstrate CaHA injection safety and effectiveness in improving the overall aesthetic appearance of the hands.

The safety evaluation indicated that no obscuration of the bones was reported on either hand (left or right) in either view (AP or lateral view) at any evaluated time point. Based on the study results, CaHA injection in the hands does not obscure the hand bones as seen on plain X-rays. The safety of multiple retreatments with CaHA in the dorsum of the hands was also demonstrated by the lack of bone obscuration after multiple retreatments.

Subjective functional outcomes were evaluated through the MHQ, a hand-specific outcomes instrument that measures outcomes of patients with conditions of, or injury to, the hand or wrist. Overall, mean MHQ function scores at the end of the study were higher than baseline showing no deterioration of functionality after CaHA injection. MHQ pain scores were lower than baseline indicating that pain did not increase after injection. The study results suggest that CaHA injections did not have a detrimental long-term effect on hand function or pain.

Furthermore, the study confirms CaHA safety and is consistent with the safety profile described in the current Radiesse instructions for use. Reported AEs were local in nature,

mostly mild or moderate in severity, and were generally unrelated to the treatment procedure with the exception of administration site conditions.

The results of the current study support the efficacy of CaHA injection in the dorsum of the hands. In general, aesthetic outcomes were similar between groups. High responder rates were reported at Month 1 and remained substantial at Month 24, which indicate long-term aesthetic improvement. GAIS analyses supported the above results, showing overall improved appearance and a long-lasting effect for the majority of subjects.

The main limitation of the study was its open-label observational design. Nevertheless, this design allowed evaluation of performance and safety of the medical device when used according to the currently approved instructions for use.

The reported results support the clinical performance and safety of CaHA injection in the hands and prove that Radiesse does not obscure the hand bones.

Conclusions

Under the conditions of this study, CaHA injection in the hands does not obscure the bones as seen on plain X-rays up to 24 months after initial injection. The safety of CaHA retreatment was also demonstrated by the lack of bone obscuration after multiple retreatments. Results support the safety and efficacy of CaHA for improving the overall aesthetic appearance of the hands.

References

1. AZ Rivkin. Volume correction in the aging hand: role of dermal fillers. Clin Cosmet Investig Dermatol. 2016;9:225-32.

2. Radiesse® Injectable Implant Instructions for Use for the Dorsum of the Hand. 2015 [Available from: https://www.radiesse.com/wp-content/uploads/Radiesse-Hands-Instructions-for-Use.pdf.

3. T Pavicic. Complete biodegradable nature of calcium hydroxylapatite after injection for malar enhancement: an MRI study. Clin Cosmet Investig Dermatol. 2015;8:19-25.

4. J Emer,H Sundaram. Aesthetic applications of calcium hydroxylapatite volumizing filler: an evidence-based review and discussion of current concepts: (part 1 of 2). Journal of drugs in dermatology : JDD. 2013;12(12):1345-54.

5. T Pavicic. Calcium hydroxylapatite filler: an overview of safety and tolerability. Journal of drugs in dermatology : JDD. 2013;12(9):996-1002.

6. R Fathi,JL Cohen. Challenges, Considerations, and Strategies in Hand Rejuvenation. Journal of drugs in dermatology : JDD. 2016;15(7):809-15.

7. JA Kadouch. Calcium hydroxylapatite: A review on safety and complications. J Cosmet Dermatol. 2017;16(2):152-61.

8. K Frank, K Koban, S Targosinski, K Erlbacher, TL Schenck, G Casabona, et al. The Anatomy behind Adverse Events in Hand Volumizing Procedures: Retrospective Evaluations of 11 Years of Experience. Plast Reconstr Surg. 2018;141(5):650e-62e.

9. M Busso,D Applebaum. Hand augmentation with Radiesse (Calcium hydroxylapatite). Dermatologic therapy. 2007;20(6):385-7.

10. S Haq, R Storck, M Baspeyras, A Thio, C Campion, E Essayagh, et al. Multinational, Multipatient Study of Calcium Hydroxylapatite for Treatment of the Aging Hand. Dermatologic Surgery. 2010;36(Sup 1):782-9.

11. MH Graivier, ZP Lorenc, LM Bass, R Fitzgerald,DJ Goldberg. Calcium Hydroxyapatite (CaHA) Indication for Hand Rejuvenation. Aesthet Surg J. 2018;38(suppl_1):S24-S8.

12. MP Goldman, A Moradi, MH Gold, DP Friedmann, K Alizadeh, JM Adelglass, et al. Calcium Hydroxylapatite Dermal Filler for Treatment of Dorsal Hand Volume Loss: Results From a 12-Month, Multicenter, Randomized, Blinded Trial. Dermatol Surg. 2018;44(1):75-83.

13. DC Wu,MP Goldman. Randomized, Double-Blinded, Sham-Controlled, Split-Hand Trial Evaluating the Safety and Efficacy of Triamcinolone Acetate Injection After Calcium Hydroxylapatite Volume Restoration of the Dorsal Hand. Dermatol Surg. 2018;44(4):534-41.

14. NS Sadick. A 52-week study of safety and efficacy of calcium hydroxylapatite for rejuvenation of the aging hand. Journal of drugs in dermatology : JDD. 2011;10(1):47-51.

15. J Valiyaparambil, K Rengasamy,SM Mallya. An unusual soft tissue radiopacity--radiographic appearance of a dermal filler. Br Dent J. 2009;207(5):211-2.

16. LW Schelke, HJ Van Den Elzen, PP Erkamp,HA Neumann. Use of ultrasound to provide overall information on facial fillers and surrounding tissue. Dermatol Surg. 2010;36 Suppl 3:1843-51.

17. A Carruthers, M Liebeskind, J Carruthers,BB Forster. Radiographic and computed tomographic studies of calcium hydroxylapatite for treatment of HIV-associated facial lipoatrophy and correction of nasolabial folds. Dermatol Surg. 2008;34 Suppl 1:S78-84.

18. A Carruthers, J Carruthers, B Hardas, M Kaur, R Goertelmeyer, D Jones, et al. A validated hand grading scale. Dermatol Surg. 2008;34 Suppl 2:S179-83.

19. JL Cohen, A Carruthers, DH Jones, VA Narurkar, M Wong, LN Cheskin, et al. A Randomized, Blinded Study to Validate the Merz Hand Grading Scale for Use in Live Assessments. Dermatol Surg. 2015;41 Suppl 1:S384-8.

20. MJ Shauver,KC Chung. The minimal clinically important difference of the Michigan hand outcomes questionnaire. The Journal of hand surgery. 2009;34(3):509-14.

Tables

Table 1: Summary of Exclusion Criteria

Exclusion Criteria
Participation in the previous Radiesse hands pivotal clinical study.
Treatment with fat injections or Radiesse in the hands, hand deformities, or surgery in the dorsum of the hands.
Dermal resurfacing procedures (within the past 6 months or during the study) or non-invasive skin-tightening in the dorsum of the hands during the study.
Prescription wrinkle therapies, topical steroids, skin-irritating topical preparations, or pigmenting agents (self-tanning agents) in the dorsum of the hands in the previous 2 weeks or during the study.
Immunosuppressive medications or systemic steroids in the previous 2 months or during the study.
Acute inflammatory process or infection, or history of chronic or recurrent infection or inflammation with the potential to interfere with the study results or increase the risk of AEs.
Known bleeding disorder or receiving medication that would likely increase the risk of bleeding as the result of injection.
Known history of allergic/anaphylactic reactions, including hypersensitivity, to lidocaine or anesthetics of the amide type, or any of the device components.
Known history of hyper- or hypo-pigmentation, keloid formation, or hypertrophic scarring.
Female of childbearing potential and not using medically effective birth control or was pregnant or lactating.
Any other medical condition with the potential to interfere with the study or increase the risk of adverse events

Table 2: Baseline demographic characteristics for all subject receiving study treatment, SES (N = 20).

	Group A (N = 10)	Group B (N = 10)	Total (N = 20)
Age [years]			
Mean (SD)	61.6 (7.40)	53.3 (9.83)	57.5 (9.48)
Sex (n (%))			
Female	10 (100.0)	10 (100.0)	10 (100.0)
Race (n (%))			
White	9 (90.0)	10 (100.0)	19 (95.0)
Two or more races	1 (10.0)	0 (0.0)	1 (5.0)
Fitzpatrick Skin Type			
I	0 (0.0)	0 (0.0)	0 (0.0)
II	6 (60.0)	4 (40.0)	5 (50.0)
III	3 (30.0)	6 (60.0)	9 (45.0)
IV	1 (10.0)	0 (0.0)	1 (5.0)

Note: SD = standard deviation; n = number of observations, N = number of subjects in corresponding group

Table 3: Treatment scheme

	Group A (N = 10) n (%)	Group B (N = 10) n (%)	Total (N = 20) n (%)
Initial Treatment Only	1 (10.0)	1 (10.0)	2 (10.0)
2 Treatments	0 (0.0)	4 (40.0)	4 (20.0)
3 Treatments	5 (50.0)	3 (30.0)	8 (40.0)
4 Treatments	4 (40.0)	2 (20.0)	6 (30.0)

Note: n = number of observations, N = number of subjects in corresponding group

Table 4: Injection volume

	Group A (N = 10) mean (SD)	Group B (N = 10) mean (SD)	Total (N = 20) mean (SD)
Initial treatment	3.34 (0.361)	2.64 (0.404)	2.99 (0.520)
Month 6 Retreatment	2.26 (0.452)	2.36 (0.528)	2.30 (0.470)
Month 12 Retreatment	2.86 (0.394)	1.87 (0.545)	2.37 (0.687)
Month 18 Retreatment	2.86 (0.394)	1.87 (0.545)	2.37 (0.687)
Cumulative Volume	9.24 (3.108)	5.96 (2.514)	7.60 (3.248)

Table 5: Bone obscuration, blinded investigator's rating, SES

Visit	Hand	X-ray view	Foreign Material Present		Any Bone Obscuration	
			n/N	(%)	n/N	(%)
Month 1	Left hand	AP view	20/20	(100.0)	0/20	(0.0)
		Lateral view	20/20	(100.0)	0/20	(0.0)
	Right hand	AP view	20/20	(100.0)	0/20	(0.0)
		Lateral view	20/20	(100.0)	0/20	(0.0)
Month 6	Left hand	AP view	17/20	(85.0)	0/17	(0.0)
		Lateral view	17/20	(85.0)	0/17	(0.0)
	Right hand	AP view	18/20	(90.0)	0/18	(0.0)
		Lateral view	16/20	(80.0)	0/16	(0.0)
Month 24[a]	Left hand	AP view	5/6	(83.3)	0/5	(0.0)
		Lateral view	5/6	(83.3)	0/5	(0.0)
	Right hand	AP view	5/6	(83.3)	0/5	(0.0)
		Lateral view	5/6	(83.3)	0/5	(0.0)

Note: [a] X-ray at Month 24 was only conducted for subjects who received 4 total treatments (initial and 3 retreatments). Further, only those hands with foreign material present in the X-ray were evaluated for any bone obscuration; AP = anteroposterior.

Table 6: Summary of Adverse Events related to device or injection, reported by treating investigators over the course of the study, SES

Adverse Event	Subjects with Event Group A (N = 10) n (%)	Subjects with Event Group B (N = 10) n (%)	Subjects with Event Total (N = 20) n (%)
Nodule	1 (10.0)	0 (0.0)	1 (5.0)
Pain	0 (0.0)	1 (10.0)	1 (5.0)
Swelling	1 (10.0)	3 (30.0)	4 (20.0)

Note: n = number of observations, N = number of subjects in corresponding group

Table 7: Summary of common treatment site responses reported in subject diaries, SES

Diary-reported term	Subjects with Event n (%)
Swelling	20 (100.0)
Redness	18 (90.0)
Bruising	17 (85.0)
Pain	16 (80.0)
Difficulty performing activities requiring the hands	9 (45.0)
Itching	8 (40.0)
Loss of ability of hands to sense hot, cold, or touch	1 (5.0)
Other[a]	5 (25.0)

Note: [a] Other events reported by 5 subjects were not serious, short in duration (≤ 3 days), and nearly all (80%) were “mild“ or “moderate“ in severity; n = number of observations

Figure Legends

Figure 1: Study design.

Figure 2: Representative X-ray images. Images represent the right hand of a subject who received four injections in the dorsum of the hands at different timepoints during the study: A) Enrollment; B) Month 1; C) Month 6; and D) Month 24.

Figure 3: Responder rates for subjects who achieved a ≥ 1 grade improvement from baseline in blinded investigator's rating according to Merz Hands Grading Scale (MHGS), SES. Note: Percentage (%) equals (n/total number of subjects [20])x100.

Figure 4: Assessment of perceived improvement after 1, 6, 12, 18 and 24 months after injection, SES. The investigator's perception of subject's improvement was assessed by a blinded investigator's live rating using the Global Aesthetic Improvement Scale (GAIS; 7-point scale ranging from "very much worse" to "very much improved").

Figures

Figure 1

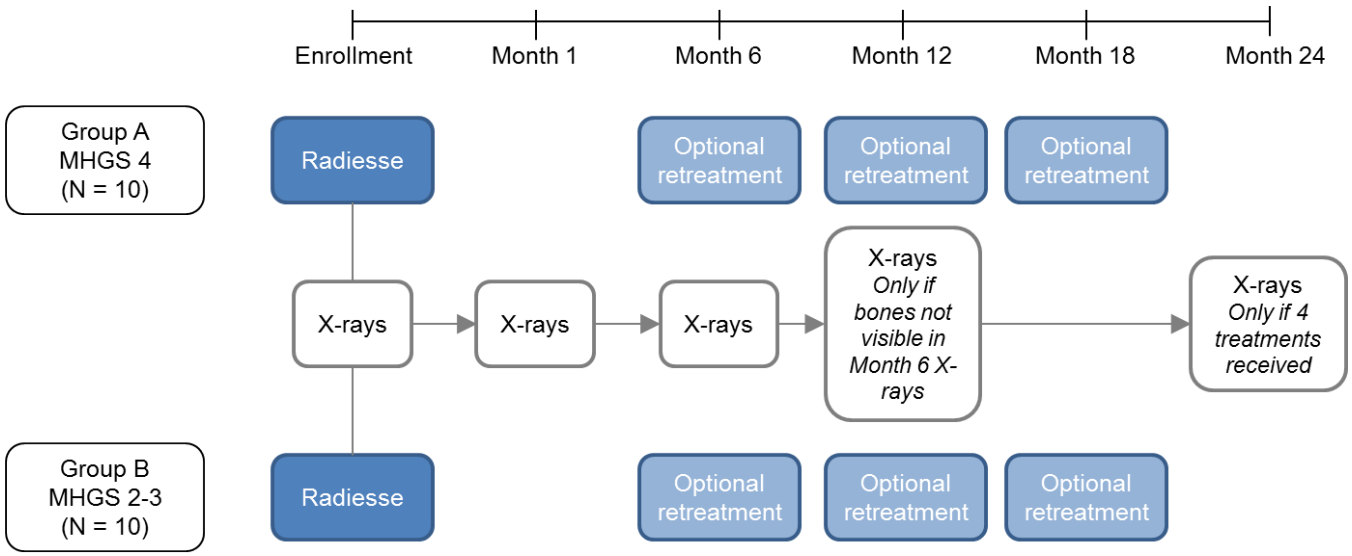


Figure 2

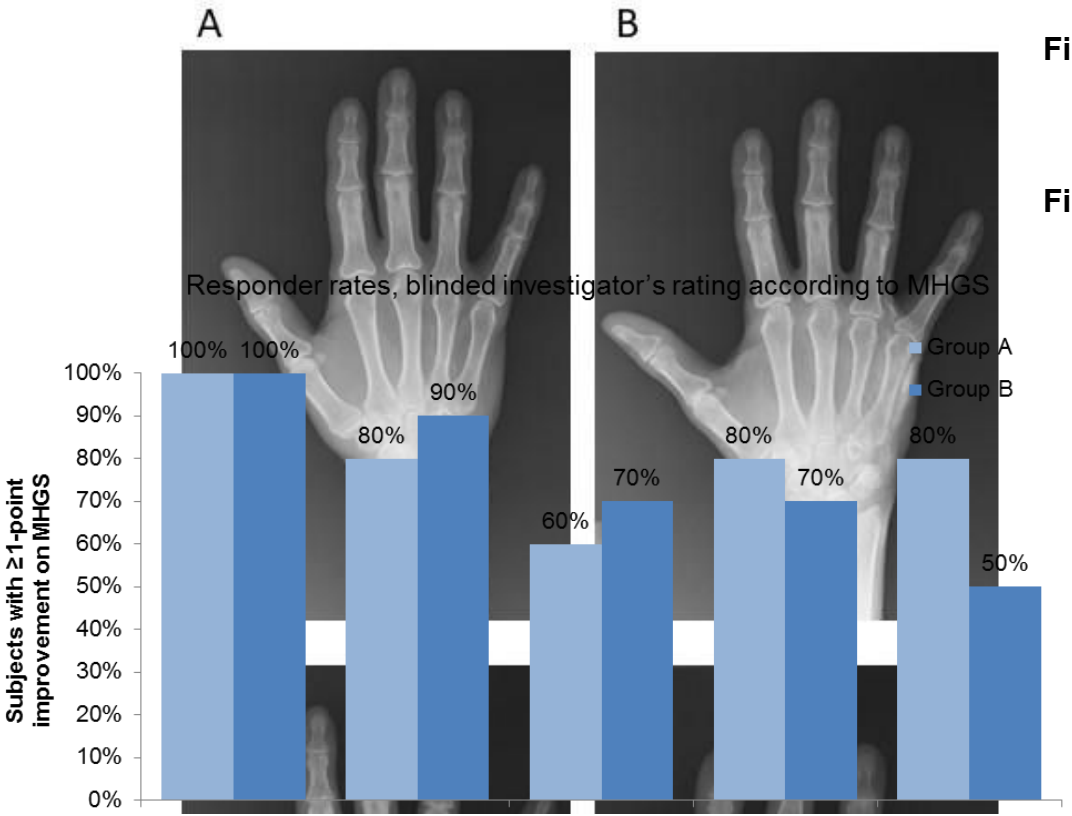
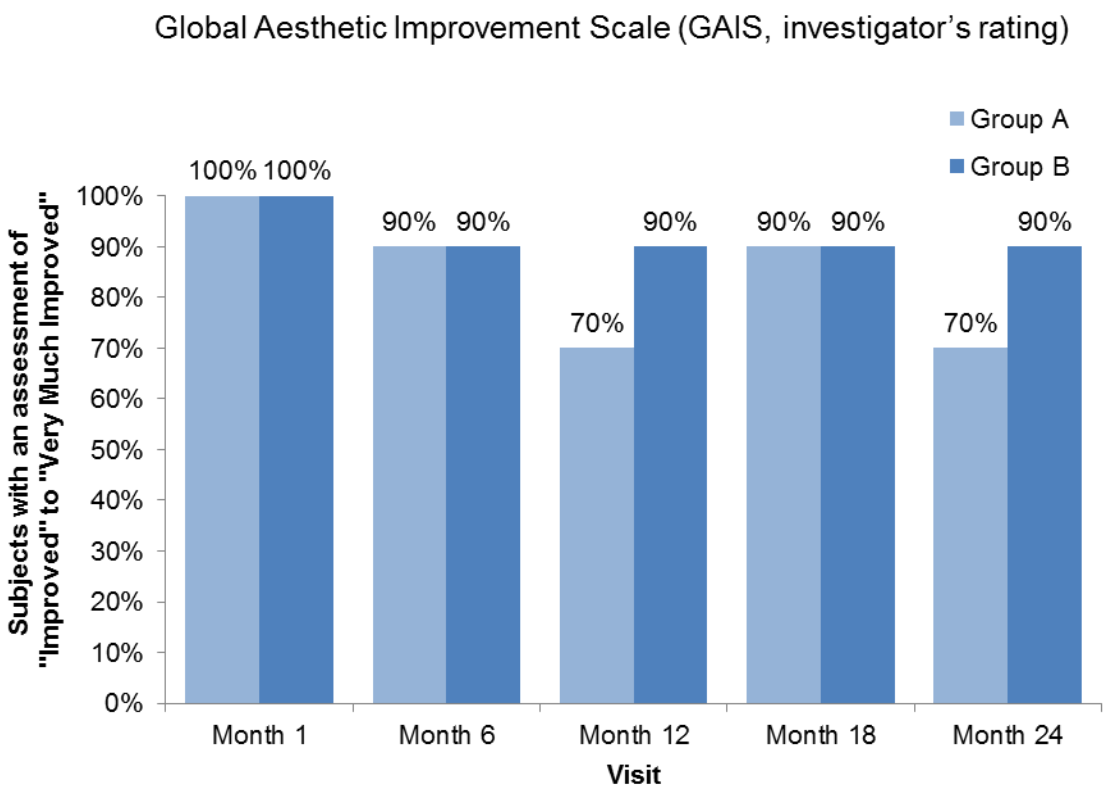


Figure 3

Figure 4


Global Aesthetic Improvement Scale (GAIS, investigator's rating)
Group A
Group B
Subjects with an assessment of "Improved" to "Very Much Improved"
100%
90%
80%
70%
60%
50%
40%
30%
20%
10%
0%
100% 100%
90% 90%
70% 90%
90% 90%
70% 90%
Month 1
Month 6
Month 12
Month 18
Month 24
Visit